REMARKS

Claims 1-14 are pending in the application. Claims 6-14 have been withdrawn from consideration by the Examiner as being directed to non-elected subject matter. Claims 2 and 5 have been canceled by applicants without prejudice or disclaimer. Claims 1, 3, and 4 have been amended. Additionally, new claims 15-17 are added herein. All of the claim amendments and new claims are entirely supported by the application as originally filed and, thus, their entry into the file of this application is respectfully requested.

As presently constituted, claims 1, 3 and 4 recite a method for treating cell necrosis or a neurodegenerative disorder associated therewith. New claims 15-17, however, recite a method for treating and/or preventing such cell necrosis or neurodegenerative disorder associated therewith.

Upon entry of this response, claims 1, 3, 4 and 15-17 will be pending in the application.

OBJECTIONS TO THE SPECIFICATION

In the Office Action, the Examiner objected to Figures 2-4 as filed as being allegedly unclear. In response, Applicants include herewith corrected drawing sheets containing the subject figures in compliance with 37 CFR 1.121(d).

Applicants therefore respectfully request withdrawal of the objection.

CLAIM REJECTIONS

Rejections under 35 U.S.C. Section 112, second paragraph

In the Office Action, the Examiner rejected claims 1 and 3-5 under 35 U.S.C. Section 112, second paragraph, alleging that these claims do not interrelate essential elements of the invention by not reciting an active step.

In response, in order to expedite prosecution but without agreeing to the correctness of the rejection, amended claim 1 recites "by means of administration of a therapeutically effective amount of one or more elastase inhibiting agents, wherein said elastase inhibitors are capable of entering said cells." Thus, claim 1 and claims 3-4, which are dependent thereupon, recite an active step. This feature is, in addition, recited in new claims 15-17.

Applicants therefore respectfully request withdrawal of the objection.

Further, the Examiner alleged that the phrase "one or more agents administered" in claim 3 lack sufficient antecedent basis.

In response, amended claim 1 contains the missing antecedent basis.

Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. Section 112, first paragraph

Further, the Examiner rejected claims 1-5 under 35 U.S.C. Section 112, first paragraph, alleging that the subject specification does not provide enablement to one skilled in the art to practice the invention. The Examiner alleged that one of ordinary skill in the art had no clear picture of the etiology of Alzheimer's Disease at the priority date of the subject application.

Applicants respectfully disagree. Amended claims 1 and 3-4 are directed to a method for treating cell necrosis or a neurodegenerative disorder associated therewith, comprising the inhibition of one or more elastase enzymes within said cell by means of administration of a therapeutically effective amount of one or more elastase inhibiting agents. Support for amended claims 1 and 3-4 is found in the claims as filed. In like manner, new claims 15-17 are, as noted above, directed to a method of treating and/or preventing such necrosis or associated neurodegenerative disorder. Support for the new claims is also present in the originally filed application.

Contrary to the Examiner's allegations, Applicants respectfully assert that one of ordinary skill in the art knew at the priority date of the subject application that

neurodegenerative disorders (e.g., Alzheimer's Disease) were caused by a final common pathway of neurotoxicity resulting in cell death, as evidenced by E. Bonfoco et al, "Apoptosis and Necrosis: Two distinct events induced, respectively, by mild and intense insults with N-methyl-D-aspartate or nitric oxide/superoxide in cortical cell cultures", *Proc. Natl. Acad. Sci.*, 92: 7162-7166 (1995). A copy of the reference is provided herewith and listed on the accompanying form PTO-1449:

> "*N*-Methyl-D-aspartate (NMDA) receptor-mediated neurotoxicity may depend, in part, on the generation of nitric oxide ($NO^{\cdot}$) and superoxide anion (O_2^{-}), which react to form peroxynitrite ($OONO^{-}$). This form of neurotoxicity is thought to contribute to a final common pathway of injury in a wide variety of acute and chronic neurologic disorders, including focal ischemia, trauma, epilepsy, Huntington disease, Alzheimer disease, amyotrophic lateral sclerosis, AIDS dementia, and other neurodegenerative diseases" (Abstract; emphasis added).

In view of the knowledge in the art that neurodegenerative disorders are caused by neurotoxicity resulting in cell death, the findings of the present invention that elastase inhibitors significantly inhibit necrosis (*inter alia* Example 5) and apoptosis (*inter alia* Example 9) in neuronal PC-12 cells would certainly enable a person of ordinary skill to make and use the claimed invention without the need for undue experimentation.

Further, claim 1 (and claim 15) recites "cell necrosis or a neurodegenerative disorder associated therewith." Even if isolated instances exist of neurodegenerative disorders not associated with cell necrosis, neither amended claim 1 nor claim 15 reads on such instances.

Further, the Examiner cited the Hingley and Solomon references to allegedly show that one of ordinary skill in the art had no clear picture of the etiology of Alzheimer's disease.

Applicants respectfully disagree, and assert that the Hingley and Solomon references should be taken in the context of the well-established knowledge in the art that neurodegenerative disorders are caused by cell death, as described above. These references merely suggest that there is uncertainty regarding the ***root causes*** of the cell

death causing the neurodegenerative disorders, as evidenced by the following quotation from Hingley:

> "While researchers now have a deeper understanding of the brain and behavioral changes characterizing the disease, Alzheimer's remains shrouded in mystery... But because so much about what triggers Alzheimer's is still unknown, developing treatment and prevention is an ongoing challenge" (Hingley, ninth paragraph, emphasis added).

Similarly, the entire disclosure of Solomon is clearly directed to attempts to prevent Alzheimer's disease by addressing the formation of amyloid plaques, a suspected root cause of the cell death underlying the disease. Solomon's statement that treatment of Alzheimer's disease requires an improved understanding of the disease should be thus taken in this context, since the root causes of the cell death were incompletely understood at the time.

Applicants respectfully assert that these references are irrelevant to the present invention. As described above, it certainly was well established as of the priority date of the present application that cell death is the underlying cause of neurodegenerative disorders. Since the presently claimed method treats the cell death itself, not the root causes of the cell death, it is not necessary to possess a full and complete understanding of the root causes of the cell death to practice the present invention. Thus, the assertion by these references that Alzheimer's disease is incompletely understood does not by itself render the art "unpredictable," particularly with regard to the present invention, which bypasses the root causes of the cell death by treating the cell death itself. Accordingly, the indicated application is enabled by the subject specification.

Further, the Examiner is respectfully reminded that enablement under 35 U.S.C. Section 112, first paragraph is assessed according to one of ordinary skill in the art, which the Examiner has admitted is "high" (Office Action, page 6). Applicants respectfully assert that the assertions of Audrey T. Hingley, described in the reference as "a freelance writer," do not reflect the level of knowledge of one of ordinary skill in the

art. Thus, Applicants respectfully assert that the Hingley reference should not have been cited against the present invention.

With regard to the Examiner's comments, e.g., on p. 5 of the Office Action, concerning the recitation of "prevention" in applicants' claims, applicants note that, as indicated above, in the present claim set claims 1, 3 and 4 recite only 'treatment', whereas new claims 15-17 are directed to 'treating and/or preventing' cell necrosis or a neurodegenerative disorder associated therewith. As to such 'prevention', applicants respectfully submit that the present invention is, *inter alia*, directed towards preventing downstream events i.e. cell death, which commonly precedes development of dementia. Even if such prevention does not constitute a 'total' prevention (i.e., per the discussion at p. 5 of the Office Action), the intervention does occur at a stage before dementia occurs and thus it serves a preventative function.

The following is a citation from P. Francis, "Targeting Cell Death in Dementia. Alzheimer Disease & Associated Disorders. 20 Supplement 1:S3-S7, April/June 2006" supporting the approach that prevention of cell death serves as a mechanism for neuroprotection against the two main causes of dementia: Alzheimer's Disease ("AD") and vascular Dementia:

> Neuronal degeneration is a key feature of both Alzheimer disease (AD) and vascular dementia (VaD). Although the exact cause(s) of neurodegeneration in AD is uncertain, strong candidates are [beta]-amyloid and neurofibrillary tangles (NFT) within neurons. VaD arises as a consequence of ischemic insults such as hemorrhage and hypoperfusion that trigger neurodegeneration by depriving the cells of oxygen and glucose. The initial insults in AD and VaD result in regional differences in the pattern of neurodegeneration ..... Although the initial trigger of neurodegeneration and the population of neurons affected differ in AD and VaD, there is considerable overlap in the downstream pathways that mediate cell death. As a consequence there are, therefore, a number of levels in the cytotoxic pathway common to AD and VaD at which a neuroprotective agent might be targeted.

In conclusion, therefore, since cell death (cellular toxicity) occurs down stream in AD and other diseases leading to dementia, halting cell death acts to prevent the dementia.

Further in support of the remarks made above, applicants are providing the Examiner with a report (attached hereto) concerning certain *in vivo* experiments which were recently undertaken by them and/or which were carried out under their direct supervision and control, which clearly illustrates the positive effects of the use of elastase inhibitors on dementia. As stated therein, "the findings clearly indicate that early administration of elastase inhibitor significantly improves neurological function, substantially reduces the necrotic infarct and improves the pathological outcome induced by the traumatic event.". If the Examiner is reluctant to consider this data in its present form, applicants are willing (if requested by the Examiner) to re-submit the subject data in the form of a declaration under 37 C.F.R. §1.132.

Thus, although in applicants' view their specification constitutes an enabling disclosure (i.e., for both 'prevention' and 'treatment') without need of any additional data, they have, nonetheless, subsequently validated the disclosure of the subject specification by demonstrating (in the experimental results provided herein) prevention of neurodegenerative disease by administration of an elastase inhibitor *in vivo*. That is, elastase inhibitor administration *in vivo* protected against necrotic cell death and neurological dysfunction, in a rat model of head trauma (See the attached experimental report). Applicants, thus, respectfully assert that their specification enables both preventing and treating neurodegenerative diseases by practice of the method(s) as recited in the present claims.

Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. Section 102

The Examiner additionally rejected claims 1-5 under 35 U.S.C. Section 102(b) in view of Gyorkos, alleging that Gyorkos teaches a method of administering an elastase inhibitor to a host in need thereof, and that such inhibitors are useful for treatment of, *inter alia*, Alzheimer's disease.

Applicants respectfully disagree. Gyorkos is directed to human neutrophil elastase (HNE), a protease that damages connective tissue cells via extracellular proteolytic

activity following its release from polymorphonuclear leukocytes, as described in Gyorkos:

> This release of HNE and its extracellular proteolytic activity are highly regulated and are normal, beneficial functions of PMNs. The degradative capacity of HNE, under normal circumstances, is modulated by relatively high plasma concentrations of α_1-proteinase inhibitor (α_1-PI). However, stimulated PMNs produce a burst of active oxygen metabolites, some of which (hypochlorous acid for example) are capable of oxidizing a critical methionine residue in α_1-PI. Oxidized α_1-PI has been shown to have limited potency as an HNE inhibitor and it has been proposed that alteration of this protease/antiprotease balance permits HNE to perform its degradative functions in localized and controlled environments (column 1 lines 24-39; emphasis added).

Gyorkos provides merely a hypothetical connection between HNE and Alzheimer's disease by making the unsubstantiated assertion that HNE and Alzheimer's disease are in some way connected. Gyorkos does not provide any data or evidence to support this hypothesis.

Thus, Gyorkos is not an enabling reference.

Further, Gyorkos differs from the presently claimed method in that Gyorkos is directed to inhibition of an extracellular protease activity. By contrast, claim 1 of the application recites "inhibition of one or more elastase enzymes within said cell." Gyorkos is not concerned with inhibition of intracellular elastase activity, as evidence by the fact that Gyorkos provides no data regarding cell permeability of the disclosed tripeptide inhibitor, and by the fact that protease inhibitory activity is assessed *in vitro* (Example 4, columns 9-10) or in cell-free supernatants (Example 5, column 10).

Overall, Gyorkos is not even similar to the methods claimed in the present application. Connective tissue damage via an extracellular protease released from a neighboring cell is a completely different process with a completely different mechanism of action than necrotic cell death of a neuron from intracellular protease activity.

Further, Gyorkos is directed to inhibition of human neutrophil elastase, an enzyme that appears specifically in neutrophils. By contrast, the present invention is directed to inhibition of an elastase enzyme inside a neuron.

Thus, the disclosure of Gyorkos is completely unrelated to the present invention. Applicants therefore respectfully request withdrawal of the rejection.

Further, the Examiner also rejected claims 1-5 under 35 U.S.C. Section 102(b) in view of Miyano, alleging that Miyano teaches a method of administering an elastase inhibitor to a host in need thereof, and that such inhibitors are useful for treatment of, *inter alia,* arthritis.

Applicants respectfully disagree. Methods of treating arthritis, as allegedly disclosed in Miyano, are completely unrelated to the present invention. Thus, the disclosure of Miyano is completely unrelated to the present invention. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. Section 103(a)

Further, the Examiner rejected claims 1-5 under 35 U.S.C. Section 103(a) in view of Gyorkos in combination with Stein, alleging that Gyorkos teaches a method of administering an elastase inhibitor to a host in need thereof, and that such inhibitors are useful for treatment of *inter alia* Alzheimer's disease, and that it would be obvious to a person of ordinary skill in the art to substitute the chloromethyl ketone peptide of Stein for the tripeptide disclosed by Gyorkos.

Applicants respectfully disagree. As described above, Gyorkos is directed to inhibition of an extracellular protease, and Gyorkos is not concerned with inhibition of intracellular elastase enzymes, nor does it disclose an agent that can act intracellularly. Further, Gyorkos is not even similar to the methods claimed in the subject application by contrast, which are directed to inhibition of one or more intracellular elastase enzymes, as described above. Prevention of extracellular degradative activity mediated by an extracellular protease released from a neutrophil is a completely different activity that prevention of necrotic cell death from intracellular proteases. Thus, Gyorkos is directed

to inhibition of human neutrophil elastase, an enzyme that appears specifically in neutrophils, and is released from neutrophils. By contrast, the present invention is directed to inhibition of an elastase enzyme inside a neuron. The alleged disclosure in Stein of the mechanism of activation of HNE by a chloromethyl ketone does nothing to remedy the fact that Gyorkos has no relevance to the present invention. Stein provides no data or evidence to connect elastase inhibitors to neurodegenerative diseases.

Information Disclosure Statement

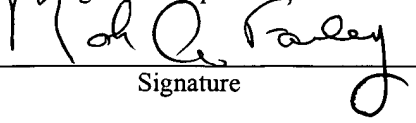
Submitted herewith is a copy of a search report issued by a patent searching authority other than the PTO and some of the cited art (the remaining references cited in the Search Report were previously submitted in an Information Disclosure Statement dated August 23, 2007), as well as some additional references, together with a form listing the same for the convenience of the Examiner.

We respectfully request that the information submitted be considered and enclose our payment of the required $180.00 fee.

In the event the actual fee is greater than the payment submitted or is inadvertently not enclosed or if any additional fee due during the pendency of this application is not paid, the Patent and Trademark Office is authorized to charge the underpayment to Deposit Account No. 15-0700.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on : March 7, 2008

Mark A. Farley
Name of applicant, assignee or Registered Representative

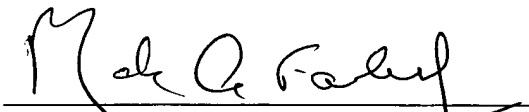


Signature

March 7, 2008
Date of Signature

MAF:jl

Respectfully submitted,



Mark A. Farley
Registration No.: 33,170
OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403
Telephone: (212) 382-0700

EXPERIMENTAL *IN VIVO* RESULTS

Introduction

The two strategies that are currently used in the management of cognitive decline in Alzheimer's disease and causes of dementia are replacement and neuroprotection. Replacement strategies focus on the neurochemical deficits in AD, such as ACh or norepinephrine, whereas neuroprotective strategies aim to retard the progression of the illness by slowing down further neuronal injury or loss. Our patent relates to the latter approach, which in other words, tries to halt neuronal cell death thereby preventing subsequent dementia.

We used the traumatic brain injury (TBI) model to study the effect of elastase inhibitors on dementia. TBI is a common neurological condition associated with neurological and psychological dysfunctions (2), it is a leading cause of morbidity and mortality as well as dementia in young people in industrialized countries (1). Traumatic injury is defined as brain damage after external head trauma. TBI is associated with cognitive and mental disabilities, in which depression is a common symptom. While cognitive impairment is common after head trauma, the severity and deficits are related to the extent and location of damage. Since there are no approved specific pharmacological agents that block the progression of secondary injury, the current management of TBI is mainly supportive.

TBI is also known to be a triggering event for a set of pathophysiological changes and concomitant cognitive deficits. Immediately following the primary impact, activation of several different pathways begins, resulting in secondary brain injury. This combination of cellular and physiologic

disturbances causes increased neuronal cell death, enlargement of infarct size, and neurological, motor, and cognitive impairment.

In the present study we used an established rat model of mild closed head injury (CHI), to assess the influence of elastase inhibitor III on the development of brain necrosis. Elastase inhibitor III was administrated prior and immediately following impact, on neurological function 1 h and 24 h after the impact was studied. The later indicates effect on secondary brain injury. Neuronal cell death was visualized by quantization of the necrotic infarct size following staining with a viable stain. The results showed that pretreatment with elastase inhibitor III inhibits TBI- induced brain necrotic cell death and attenuates impairment of neurological function.

Experimental methods

Animals and Traum Model

The study was performed according the guidelines of the Institutional Animal Care Committee of Ben-Gurion University.

Sprague–Dawley rats weighing 311 ± 32.46 g (mean ± standard deviation (SD)) were used. Experimental mild TBI (mTBI) was performed , using a weight-drop device described previously. The weight-drop device was used to deliver a standard shock to the cranium resulting in a controlled cerebral injury. Impact was delivered by a silicone-coated 5-mm metal tip extruding from a platform that falls down a frame. The hemisphere ipsilateral to the impact displays a hemorrhagic contusion that develops into an area of hemorrhagic necrosis 18 hours post injury. This model of cranial injury has been used in multiple previous studies (3-5).

Compound

Elastase inhibitor III was purchased from Sigma. It was dissolved in 20% DMSO in saline to a concentration of 12 and 20 mM which will be referred to as solution 1 and solution 2, respectively. Rats were injected with 20 μL of 12 mM of elastase inhibitor III (treatment 1) or with 20 mM (treatment 2). The controls were injected with 20 μL of the solvent only (20% DMSO in saline). These solutions were unilaterally intracerebroventriculary injected (i.c.v.). The estimated final concentration of elastase inhibitor III was 300 and 500 μM in CSF given that the CSF volume was approximately 700 μL. Two i.c.v. injections were performed in treated and control rats: the first 10 minutes before the trauma and the second 15 minutes after the trauma.

Surgery Procedure

Rats were assigned randomly to one of the experimental groups.

Rats were prepared for surgery by anesthetization with isoflurane and were allowed to breath spontaneously. Maintenance of adequate anesthesia for the experimental procedure was confirmed by loss of corneal reflexes. Once the corneal reflexes were abolished, a midline scalp incision was made and the scalp and underlying muscles were reflected laterally. Closed head trauma (CHT) was delivered to the skull over the frontal portion of the left cerebral hemisphere via a weight-drop device. After scalp incision with or without CHT, anesthesia was discontinued, animals were returned to their cages, and unlimited food and water were supplied. Rats that were anesthetized only and their skull subsequently exposed served as sham controls. Following

CHT, 2 rats became apneic and died. These rats were excluded from the study.

Assessment of Neurological Status

The neurological status of the rats was assessed using the neurological severity score (NSS). The following parameters were measured:

1) Exit - inability to exit from a circle 50 cm in diameter when placed in center during 5 minutes

2) Hemiplegia - inability to resist forced changes in position

3) Straight walking - inability to walk straight when placed on the floor

4) Move - inability to move

5) Tail reflex - flexion of hindlimb when raised by the tail

6) Startle - loss of startle reflex

7) Righting - loss of righting reflex

8) Seek - loss of seeking behavior

9) Prostration

Failure in beam-walking task:

10) 8.5 cm wide

11) 5.0 cm wide

12) 2.5 cm wide

Failure in beam-balancing task (1.5 cm wide)

13) for 20 sec

14) for 40 sec

15) for 60 sec

16) all limbs on beam

The NSS determines the clinical condition of the rat following CHT, with a score of 0 indicating no neurological deficit and a score of 16 indicating the

most severe impairment. The NSS was determined 1 h and 24 h after the head injury. All p-values were calculated using the Mann-Whitney test.

Determination of necrotic infarct area

Brain was sliced and stained with 1% w/w solution of 2, 3, 5-triphenyl-2H-tetrazolium chloride (TTC) at 37°C for 15 min. The slices were then scanned and the necrotic area was measured. TTC acquires a red color because mitochondrial enzymes reduce the colorless TTC to a red, water-insoluble formazan deposit. Pan-necrotic areas remain uncolored, which enables quantitation of experimental brain injury by optical scanning and image analysis of serial slices to determine the relative volume of red versus infarcted, non-stained, tissue.

Experimental Protocol

Rats were assigned randomly to one of three experimental groups. Rats in group 1 were treated with the vehicle only. Two additional groups were treated with solution 1 and 2 as described in the "compound" section. One hour after induction of mTBI, the functional status of the rat, which reflects the severity of injury, was evaluated using the NSS. After 24 h, NSS was determined and rats were killed, decapitated and their brain was sliced and stained with TTC to evaluate the necrotic area. Sham controls were tested and sacrificed at the same time points as the mTBI mice.

Results

Sham control rats were found to be healthy with an NSS of 0 to 1. No necrotic brain tissue was found in brains of rats treated with solvent or elastase inhibitor III after 24 h, as assessed by TTC staining.

Seven rats which were treated with the vehicle only had an NSS of 9.4±1 one hour after trauma.

Seven rats treated with solution 1 had an NSS of 4.85 ± 1.3 one hour after trauma

Five rats treated with solution 2 had an NSS of 5.6 ± 2.3 one hour after trauma

Seven rats which were treated with the vehicle only had an of NSS 5.0 ± 1.2 24 hour after trauma

Seven rats treated with solution 1 had an NSS of 3.6 ± 2.1 24 hour after trauma

Five rats treated with solution 2 had an NSS of 3.0 ± 1.2 24 four hour after trauma

As the results indicate, rats treated with elastase inhibitor show significantly better neurological functioning. One hour after the injury rats treated with solution 1 of elastase inhibitor rats had significantly better neurological results (NSS) than control ones (p value = 0.001), and those treated with solution 2 had a p-value of 0.005 compared to controls. These findings indicate that treatment with 300 μM gives better results in protection from neurological dysfunction at short periods after trauma

24 hours after trauma the severity of neurological defects declined in all rats. It is worth mentioning that time of renewal of CSF is approximately 15-20 minutes.

There was no significant difference between the control and the treatment 1 group. But the solution 2-treated group, those which received a higher dose

of elastase inhibitor, had significantly better neurological functions with a p value of 0.018.

The most prominent protective effect of elastase inhibitor III was observed in their seeking behavior (66%), straight walking (72%), beam balancing ability and beam walking 5.0 cm (80%). The percentage indicates improvement in performing motor tasks.

TTC staining showed significant differences between the control and the treatment 1 group. In the control group the necrotic area was 61.6 % ± 13.9 (SE) of the hemisphere area, while in the treatment 1 group the necrotic area was 8.5 %± 1.55 (SE) of the hemisphere area. P value = 0.003 . There was no significant difference between the control and the treatment 2 group (38% ± 17.4 % SE).

Conclusion

The findings clearly indicate that early administration of elastase inhibitor significantly improves neurological function, substantially reduces the necrotic infarct and improves the pathological outcome induced by the traumatic event.

References

1) Neugroschl JA, Kolevzon A et al. Dementia. In: Sadock BJ and Sadock VA, editors. Comprehensive textbook of Psychiatry, Eight edition, New York: Wiley-Liss; 2000. p. 1089

2) Milman A, Rosenberg A et al, Mild traumatic brain injury induces persistent cognitive deficits and behavioral disturbance in mice. J. Neurotrauma 22; 1003-1010, 2005

3) Levine HS, Cognitive function outcomes after traumatic brain injury. Curr. Opin. Neurol. 11; 643-646, 1998

4) Shapira Y, Shohami E, Sidi A, et al: Experimental closed head injury in rats: mechanical, pathophysiologic, and neurologic properties. Crit Care Med 16:258–265, 1988

5) Shapira Y, Setton D, Artru AA, et al: Blood-brain barrier permeability, cerebral edema, and neurologic function after closed head injury in rats. Anesth Analg 77:141–148, 1993

6) Feldman Z, Gurevittch B et al, Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. Neurosurg. 85; 131-137, 1996